L7 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:27785 CAPLUS
DOCUMENT NUMBER: 126:126801
TITLE: **Metanicotine**: A nicotinic agonist with central nervous system selectivity-in vitro and in vivo characterization
AUTHOR(S): Lippiello, P. M.; Bencherif, M.; Caldwell, W. S.; Arrington, S. R.; Fowler, K. W.; Lovette, M. E.; Reeves, L. K.
CORPORATE SOURCE: Res. and Development, R.J. Reynolds Tobacco Co., Winston-Salem, NC, 27102, USA
SOURCE: Drug Development Research (1996), 38(3-4), 169-176
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A growing body of evidence suggests that disruption of nicotinic cholinergic systems may be an important factor in the etiol. of a number of different diseases, ranging from neurodegenerative diseases, such as **Alzheimer**'s and parkinson's, to ulcerative colitis. The mechanistic basis for such diverse nicotinic effects is likely to lie in the ever growing number of potential receptor subtypes. Therefore, the development of receptor subtype-selective probes is essential to understand the emerging complexity of nicotinic cholinergic systems and the mechanisms underlying diseases that may involve these systems. Toward this end, we have evaluated the nicotinic agonist **metanicotine**, (E)-N-methyl-4-(3-pyridinyl)-3-butene-1-amine, using the following in vitro and in vivo methods: (1) receptor binding and up-regulation, (2) neurotransmitter release and ion flux in synaptosomes/cells, (3) in vivo microdialysis in rats, (4) reversal of scopolamine-induced amnesia in a step-through passive-avoidance paradigm, (5) water maze performance in mice, (6) radial-arm maze performance in brain-lesioned rats, (7) changes in heart rate and blood pressure, and (8) physiol. depression of body temperature, locomotor activity, acoustic startle, and respiration rate. Our in vitro results indicate that **metanicotine** binds with high affinity to the major receptor subtype in brain ($\alpha 4\beta 2$), evokes dopamine release from striatal synaptosomes and Rb+ efflux from thalamic synaptosomes, but does not activate ganglionic, muscle, or other peripheral type nicotinic receptors. These results suggest that **metanicotine** is selective for $\alpha 4$-containing central nervous system (CNS) nicotinic receptors and has reduced selectivity for peripheral nervous system (PNS) receptor subtypes. These conclusions are further supported by in vivo studies with **metanicotine** showing enhanced cognitive effects and significantly lower peripheral effects. Our in vivo results indicate that **metanicotine** increases the release of acetylcholine, norepinephrine, dopamine, and serotonin in cortex and is equal to or better than nicotine on measures of cognitive enhancement. By comparison, **metanicotine** is significantly less potent than nicotine in increasing heart rate and blood pressure and in causing physiol. depression. These results are consistent with in vitro data indicating **metanicotine**'s CNS receptor selectivity, and they suggest that this ligand may be a suitable tool for probing the relationships that underlie the complex central and peripheral pharmacol. of nicotinic cholinergic systems. Furthermore, **metanicotine** may be a good lead candidate for developing nicotinic agonists as CNS therapeutics with reduced peripheral side effects.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:495170 CAPLUS
DOCUMENT NUMBER: 133:237818
TITLE: A concise synthetic pathway for trans-**metanicotine** analogues

AUTHOR(S): Park, Haeil; Jang, Jinhee; Sin, Kwan Seog
CORPORATE SOURCE: College of Pharmacy, Kangwon National University, Chunchon, 200-701, S. Korea
SOURCE: Archives of Pharmacal Research (2000), 23(3), 202-205
CODEN: APHRDQ; ISSN: 0253-6269
PUBLISHER: Pharmaceutical Society of Korea
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:237818

AB A convenient pathway for synthesis of trans-**metanicotine** analogs was developed. Trans-**metanicotine**, a subtype(α4β2)-selective ligand for neuronal nicotinic acetylcholine receptor, is under clin. phase for **Alzheimer**'s disease. Zn-mediated allylation of allyl bromide and acetaldehyde followed by Heck reaction with 3-bromopyridine gave 5-pyridin-3-yl-pent-4-en-3-ol. Tosylation of 5-pyridin-3-yl-pent-4-en-3-ol followed by substitution reaction with methylamine in sealed tube gave methyl-(1-methyl-4-pyridin-3-yl-but-3-enyl)-amine in good yields. Thus, trans-**metanicotine** analogs modified at the α-position of the methylamino group with various functional groups can be obtained in 4 steps.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:11549 CAPLUS
DOCUMENT NUMBER: 136:247729
TITLE: Synthesis of (±)-methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl)-amines
AUTHOR(S): Jang, Jinhee; Sin, Kwan Seog; Park, Haeil
CORPORATE SOURCE: College of Pharmacy, Kangwon National University, Chunchon, 200-701, S. Korea
SOURCE: Archives of Pharmacal Research (2001), 24(6), 503-507
CODEN: APHRDQ; ISSN: 0253-6269
PUBLISHER: Pharmaceutical Society of Korea
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Trans-**Metanicotine**, a subtype (α4β2)-selective ligand for neuronal nicotinic acetylcholine receptor, is under clin. phase for **Alzheimer**'s disease. An efficient synthetic route for (±)-methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl)-amines, derivs. of trans-**metanicotine**, was explored. Allylation reaction of aryl aldimines with allyl magnesium bromide in THF gave (±)-methyl-(1-aryl-but-3-enyl)-amines. Protection of the amines with the Boc group and following Heck reaction of the N-Boc amines with 3-bromopyridine gave (±)-methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl)-carbamic acid tert-Bu esters. Deprotection of the N-Boc group in aqueous 1N-HCl solution gave the titled amines in good yields. Thus, trans-**metanicotine** analogs modified at the α-position of the methylamino group with aryl groups were obtained in 5 steps.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:116902 CAPLUS
DOCUMENT NUMBER: 132:161263
TITLE: Pharmaceutical composition using a nicotinic compound and an acetylcholinesterase inhibitor for the prevention and treatment of central nervous system disorders
INVENTOR(S): Bencherif, Merouane
PATENT ASSIGNEE(S): R.J. Reynolds Tobacco Co., USA
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000007600	A1	20000217	WO 1999-US12243	19990602
W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6218383	B1	20010417	US 1998-130498	19980807
CA 2335012	AA	20000217	CA 1999-2335012	19990602
AU 9943285	A1	20000228	AU 1999-43285	19990602
AU 761087	B2	20030529		
BR 9912805	A	20010502	BR 1999-12805	19990602
EP 1102588	A1	20010530	EP 1999-965348	19990602
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002522390	T2	20020723	JP 2000-563285	19990602

PRIORITY APPLN. INFO.: US 1998-130498 A 19980807
WO 1999-US12243 W 19990602

AB A pharmaceutical composition incorporates a pharmaceutically effective amount of at least two components, one of those components being a nicotinic compound capable of interacting with nicotinic cholinergic receptors (e.g., a nicotinic agonist, such as E-**metanicotine**) and one of those components being an acetylcholinesterase inhibitor (e.g., tacrine). The pharmaceutical composition is useful for treating CNS disorders, e.g. **Alzheimer**'s disease.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:816502 CAPLUS
DOCUMENT NUMBER: 135:340964
TITLE: Imaging of nicotinic acetylcholine receptor subtypes
INVENTOR(S): Bencherif, Merouane; Miller, Craig Harrison; Dull, Gary Maurice; Bhatti, Balwinder Singh; Caldwell, William Scott
PATENT ASSIGNEE(S): Targacept, Inc., USA
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001082978	A2	20011108	WO 2001-US13950	20010501
WO 2001082978	A3	20020801		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,				

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-562485 A 20000501

AB Compds. useful as probes for determining the relative number and/or function of specific receptor subtypes are claimed. Of particular interest are nicotinic agonists and antagonists (e.g., **metanicotine**-type compds. and azaadamantane-type compds.) that are selective to certain nicotinic receptor subtypes. Those compds. are labeled with a radioactive isotopic moiety such as 11C, 18F, 76Br, 123I or 125I. Central nervous system disorders are diagnosed by administering to a patient a detectably labeled compound, and detecting the binding of that compound to selected nicotinic receptor subtypes (e.g., alpha 7 and/or alpha 4 beta 2 receptor subtypes). The compds. that have been administered are detected using methods such as position emission topog. (PET) and single-photon emission computed tomog. (SPECT). The present invention is useful in the diagnosis of a wide variety of CNS diseases and disorders, including **Alzheimer**'s disease, Parkinson's disease and schizophrenia.

L7 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1996:551339 CAPLUS

DOCUMENT NUMBER: 125:185904

TITLE: Pharmaceutical compositions with aryl-substituted compounds, and their preparation, for prevention and treatment of central nervous system disorders

INVENTOR(S): Bencherif, Merouane; Lippiello, Patrick Michael; Caldwell, William Scott; Dull, Gary Maurice

PATENT ASSIGNEE(S): R.J. Reynolds Tobacco Company, USA

SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

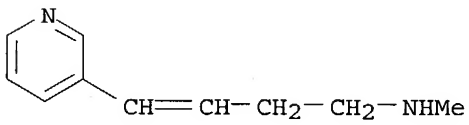
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9620600	A1	19960711	WO 1995-US17034	19951228
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5597919	A	19970128	US 1995-364979	19950106
US 5731314	A	19980324	US 1995-364978	19950106
US 5824692	A	19981020	US 1995-364977	19950106
AU 9646108	A1	19960724	AU 1996-46108	19951228
EP 801527	A1	19971022	EP 1995-944268	19951228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
JP 2001520628	T2	20011030	JP 1996-521171	19951228
US 5885998	A	19990323	US 1998-23040	19980212
US 6107298	A	20000822	US 1999-267553	19990312

PRIORITY APPLN. INFO.:
US 1995-364977 A1 19950106
US 1995-364978 A1 19950106
US 1995-364979 A1 19950106
WO 1995-US17034 W 19951228
US 1998-23040 A3 19980212

OTHER SOURCE(S): MARPAT 125:185904

AB Patients susceptible to or suffering from central nervous system disorders (e.g., Tourette's syndrome, attention deficit disorder, or schizophrenia) are treated by administering an effective amount of an aryl-substituted aliphatic compound, an aryl-substituted olefinic amine compound, or an aryl-substituted acetylenic compound Exemplary compds. are

ANSWER 27 OF 27 REGISTRY COPYRIGHT 2004 ACS on STN
RN 538-79-4 REGISTRY
CN 3-Buten-1-amine, N-methyl-4-(3-pyridinyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Metanicotine (6CI)**
CN Pyridine, 3-[4-(methylamino)-1-butenyl]- (7CI, 8CI)
OTHER NAMES:
CN NSC 66331
FS 3D CONCORD
MF C10 H14 N2
CI COM
LC STN Files: ADISINSIGHT, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, DDFU, DRUGU, EMBASE, IPA, MEDLINE, NAPRALERT, RTECS*, SYNTHLINE, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

63 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
64 REFERENCES IN FILE CAPLUS (1907 TO DATE)
18 REFERENCES IN FILE CAOLD (PRIOR TO 1967)